SANAMED
2025; 20(1): 81–88
ISSN-1452-662X

DOI: 10.5937/sanamed0-56299
UDK: 616.8-009.7
ID: 168359177
Review article

NEUROPATHIC PAIN: CHALLENGES AND SOLUTIONS IN CLINICAL PRACTICE

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Primljen/Received: 25. 01. 2025. Prihvaćen/Accepted: 25. 02. 2025. Online First: 17. 03. 2025.

Abstract: Neuropathic pain is caused by abnormal processing of signals in the peripheral and central nervous systems. It is characterized by pain occurring without external stimulation or long after the injury has passed. Typically, it is chronic, with patients describing it as burning, stinging, stabbing, or tingling. Causes include diabetes, herpes zoster, surgery, stroke, multiple sclerosis, tumors, and injuries. Despite significant advances in neuropathic pain research in recent years, therapeutic options remain limited and often insufficiently effective. Symptomatic therapy for neuropathic pain is based on the use of drugs from four basic groups: antidepressants, anticonvulsants, local analgesics, and opioids. In addition to pharmacological methods, non-pharmacological interventions are also used in the treatment of neuropathic pain. A combination of these methods with pharmacological therapy often yields the best results.

Keywords: Neuropathic pain, Clinical presentation, Diagnosis, Therapy.

INTRODUCTION

According to the International Association for the Study of Pain (IASP), neuropathic pain (NeuP) is defined as pain resulting directly from damage or disease of the somatosensory system (1). The prevalence of NeuP is estimated at 7-10% of the global population, making it a significant public health issue (2). Treatment often involves the use of antidepressants and anticonvulsants, which are sometimes ineffective. As a result, new therapies, such as selective sodium channel antagonists and monoclonal antibodies, are being investigated (3). Rehabilitation and cognitive-behavioral therapy, supported by the environment and the active involvement of the patient, are key components of an integrated therapeutic approach to this complex chronic pain condition.

Definition of Neuropathic Pain

Neuropathic pain is caused by dysfunction or injury to the somatosensory system, which transmits sensations such as touch, temperature, and pain. Depending on whether the somatosensory component of the central or peripheral nervous system is affected, NeuP is categorized into two main types: central and peripheral NeuP (1). Peripheral NeuP results from damage to peripheral nerves, with common examples including diabetic neuropathy, postherpetic neuralgia, radiculopathy, and trigeminal neuralgia. In contrast, central NeuP is caused by lesions or diseases of the central somatosensory nervous system, with common causes being spinal cord injuries, stroke, brain injuries, and multiple sclerosis.

Nociplastic pain, a newer term defined by the IASP in 2017, refers to pain resulting from altered nociception without evidence of existing or potential tissue damage that would activate peripheral nociceptors or indicate disease or damage to the somatosensory system (4). Understanding the different types of pain, including neuropathic and nociplastic pain, is crucial for proper diagnosis and selection of appropriate therapy.

Classification of Neuropathic Pain

According to the 2008 grading system, NeuP is classified into three categories: possible, probable, and definite. Possible NeuP refers to the existence of pain with the incidence of a lesion or disease of the nervous system, with pain distribution in the corresponding anatomical region. Probable NeuP is characterized by

pain accompanied by sensory signs in the corresponding neuroanatomical region, confirmed by a neurological examination. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system, confirmed by appropriate diagnostic tests. This classification systemfacilitates more accurate diagnosis and a more adequate selection of therapy for patients with NeuP (5).

Pathophysiology and Mechanisms of Neuropathic Pain

Neuropathic pain arises from lesions or dysfunctions in the peripheral or central nervous system, leading to aberrant processing of nociceptive signals (6). Key mechanisms involved include peripheral and central sensitization, ectopic activity of damaged nerve fibers, neuroinflammation, and reduced pain inhibition at the spinal cord level (7).

Peripheral sensitization occurs due to increased excitability of primary afferent neurons, with enhanced expression of sodium channels (e.g., Nav1.7, Nav1.8) and reduced activity of potassium channels (e.g., Kv1.1). This results in spontaneous firing of nerve fibers and increased sensitivity to stimuli (8).

Central sensitization, which develops in response to chronic afferent stimulation, involves enhanced activation of NMDA receptors, dysfunction of inhibitory interneurons, and increased release of pro-inflammatory cytokines, leading to abnormal pain perception.

Neuroinflammation, mediated by microglia and astrocytes, further contributes to heightened neuronal excitability and long-term changes in pain pathways (9).

These mechanisms collectively lead to phenomena such as **hyperalgesia** (increased sensitivity to pain) and **allodynia** (pain caused by non-painful stimuli), which are characteristic of neuropathic pain (10).

Clinical aspects of neuropathic pain

Neuropathic pain is a complex condition manifested by a wide range of clinical symptoms, including spontaneous pain, hyperalgesia, allodynia, and phantom pain (6). A detailed neurological examination is key to identifying the neuropathic component of pain, with an emphasis on recognizing "positive" and "negative" symptoms.

Spontaneous pain is the basic symptom of NeuP, where the painful sensation occurs without an obvious cause. This type of pain is often intense, long-lasting, and significantly impairs the patient's quality of life (11).

Hyperalgesia means an increased response to painful stimuli and is often the result of peripheral and central sensitization. It is common in the early stages of NeuP, especially after injuries to the nervous system or surgical interventions, and can last for weeks (12).

Allodynia is a painful response to painless stimuli, such as light touch or gentle pressure, and is associated with central sensitization which increases the sensitivity of the nervous system to stimuli that normally do not cause pain.

Phantom pain is a specific form of NeuP that occurs in patients after amputation. Its development is associated with neuroplasticity, whereby the reorganization of the central nervous system causes erroneous signals and painful sensations (13).

Recent research emphasizes the importance of an individualized approach in the treatment of NeuP, due to the diverse clinical manifestations and mechanisms that contribute to this condition (14). Frequently present comorbidities, such as anxiety and depression, further worsen the quality of life of patients, which indicates the need for a holistic and multidisciplinary approach to diagnosis and therapy (15).

Diagnosis of neuropathic pain

The diagnosis of neuropathic pain (NeuP) is based on a comprehensive approach that includes a detailed history, physical and neurological examination, laboratory analysis, electrophysiological testing, application of advanced imaging methods, and, in exceptional cases, skin or nerve biopsy. Given that pain is a subjective phenomenon, a key role in diagnosis is played by the patient's perception of pain, including its localization, distribution, intensity, quality, temporal dynamics, and factors affecting pain (1).

Validated unidimensional scales such as the Visual Analog Scale (VAS), Numerical Scale (NS), Verbal Scale (VS), and Facial Expression Scale are used to assess pain intensity. In addition, multidimensional tools such as the *Douleur Neuropathique 4 Questions* (DN4), *painDETECT Questionnaire*, and *Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs* (S-LANSS) provide additional information about localization, the impact of pain on daily activities, mood, and the overall quality of life of patients (16).

Neurological examination often provides crucial information about the presence of "positive" or "negative" symptoms of NeuP, but alone is not sufficient to determine the etiology and extent of damage. Electrophysiological testing, including electromyoneurography (EMNG) and somatosensory evoked potentials (SSEP), helps localize and quantify damage to peripheral and central nerve pathways. However, these methods are not useful for the diagnosis of thin fiber

neuropathy, where quantitative sensory testing (QST) and laser-evoked potentials (LEP) are used. The LEP method enables a selective assessment of nociceptor function, with a high degree of sensitivity in detecting neuropathy of thin fibers (17, 18).

In cases of normal neurological and electrophysiological findings, a skin biopsy can confirm a decrease in the density of intraepidermal C-fibers, which is diagnostically significant, although the degree of decrease does not correlate with pain intensity (19). Additional methods, such as corneal confocal microscopy and the sudomotor axon-reflex test, are still used for research purposes and are not routinely available (20, 21).

Advanced functional neuroimaging techniques, such as PET and fMRI, provide insight into regional changes in blood flow and metabolic activity in the brain, including thalamic dysfunction and asymmetric activity of the somatosensory cortex in patients with NeuP (9). In rare cases, additional tests such as immunological blood tests and cerebrospinal fluid analysis (CSF) may be needed for a precise diagnosis of NeuP.

This multidisciplinary approach enables not only the confirmation of the diagnosis but also a better insight into the basic mechanisms of NeuP, which is essential for the individualization of therapy and the improvement of the patient's quality of life.

Treatment of neuropathic pain

The treatment of NeuP requires a comprehensive, multidisciplinary, and multimodal approach due to the complex mechanisms of origin and different localizations of damage to the nervous system. Therapy includes a combination of pharmacological and non-pharmacological methods to alleviate symptoms, improve functionality, and improve the quality of life of patients (Table 1).

Antidepressant drugs in the treatment of neuropathic pain

Antidepressants, especially tricyclic antidepressants (TCAs) and duloxetine have a significant role in

Table 1. *Treatment of neuropathic pain (revised by reference 12)*

Medicine	Starting dose	Maintenance dose	Maximum daily dose	Recommendations
Tricyclic antidepressants (TCAs)				
Amitriptyline	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Nortriptyline	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Imipramine	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Selective noradrenaline/serotonin uptake inhibitors (SNRI/SSRI)				
Duloxetine	1x30 mg, in the morning	1x60 mg/d, in the morning	120 mg	First line
Venlafaxine	1x37.5 mg, in the morning	150-225 mg/d, in the morning	375 mg	First line
Anticonvulsants				
Pregabalin	1x25-50 mg, evening	150-300 mg/d	2x300 mg	First line
Gabapentin	3x100 mg/d, starting dose in the evening	1200-2400 mg/d	3x1200 mg	First line
Carbamazepin	200-400 mg/d	600-800 mg/d	1200 mg/d	First line (N. trigeminus)
Opioids				
Morphin	2x10-30 mg/d	Individual	240 mg/d	Third line
Oxycodone	2x5-10 mg/d	Individual	120 mg/d	Second line
Tramadol retard	2x50-100 mg/d	Individual	2x200 mg/d	Second line
Topical medications				
Lidocaine 5% patch	1-3 patch/d	1-3 patch/d	3 patch	Second line
Capsaicin 8% patch	1-4 patch/3 months	1-4 patch /3 months	1-4 patch /3 months	Second line

the treatment of NeuP due to their unique analgesic mechanism involving modulation of descending inhibitory pain pathways (22). Their efficacy has been confirmed in several clinical conditions, including painful diabetic neuropathy (23), postherpetic neuralgia (24), and central pain after stroke (25). These drugs not only relieve pain but do so independently of their antidepressant effect, which makes them suitable for patients with and without comorbid depression (15). Personalizing the therapeutic approach is essential to achieving the best results, taking into account the individual characteristics of patients, their comorbidities, and drug tolerance. Initial lower doses and a gradual increase to the maximally tolerated and effective dose enable the safe use of these drugs, while continuous monitoring of the therapeutic response and potential side effects contributes to the success of the treatment. For example, duloxetine is often used in the treatment of NeuP in patients with painful diabetic neuropathy because of its more favorable side effect profile compared to TCAs, although doses above 60 mg daily do not provide additional benefits in pain relief (26, 27). Venlafaxine, despite its potential utility in specific conditions such as chemotherapy-induced polyneuropathy and painful diabetic polyneuropathy, currently has limited use in NeuP therapy and requires further research to determine its precise role (28, 29).

Anticonvulsants in the treatment of neuropathic pain

The use of anticonvulsants in NeuP therapy represents a key segment of a multidisciplinary approach to this complex clinical condition. Their effectiveness is based on specific mechanisms of action that enable the reduction of the transmission of pain signals and the modulation of neuronal excitability. Gabapentin and pregabalin, voltage-gated calcium channel inhibitors, have been shown to reduce the release of excitatory neurotransmitters such as glutamate, thus successfully treating conditions such as postherpetic neuralgia, painful diabetic neuropathy, and central NeuP. Gabapentin is effective up to 3600 mg per day, while pregabalin offers added benefits in patients with insomnia and anxiety at doses up to 600 mg daily. (30,31,32). Carbamazepine and oxcarbazepine, anticonvulsants that act by blocking voltage-gated sodium channels, are particularly useful in the treatment of trigeminal neuralgia and painful diabetic neuropathy. Their action is based on the stabilization of neuronal membranes and the inhibition of the generation of ectopic impulses, with proven results at doses up to 1200 mg per day for carbamazepine (33). Lamotrigine, although primarily intended for epilepsy, has a significant role in the treatment ofhuman immunodeficiency virus (HIV)-related neuropathy and central NeuP after stroke. Other anticonvulsants, such as topiramate, lacosamide, and valproic acid, have also shown potential efficacy, especially in painful diabetic neuropathy, but their use requires further research and more clearly defined protocols (31, 32). Although anticonvulsants bring significant relief to patients with NeuP, their use requires careful dose titration and regular monitoring of side effects, especially in elderly patients and people with comorbidities. Common side effects include sedation, dizziness, edema, and weight gain, necessitating individualization of therapy to achieve an optimal balance between efficacy and safety (30, 31). Further research is necessary to improve the understanding of the molecular mechanisms of action of anticonvulsants and to define new strategies for their use.

Topical drugs in the treatment of neuropathic pain

Topical drugs represent a significant therapeutic option for localized NeuP, allowing direct application to the painful site and minimizing the risk of systemic side effects and interactions with other drugs. Lidocaine, in the form of a 5% patch, acts by blocking voltage-dependent sodium channels in afferent Aδ and C fibers, thereby effectively reducing pain (34). Capsaicin, available as a 0.075% cream or high-concentration patch (8%), acts by activating transient receptor potential(TRPV1) receptors, causing temporary depolarization and desensitization of sensory neurons (35).

Botulinum toxin

Botulinum toxin (BoNT-A) has been investigated in painful diabetic neuropathy (36), postherpetic neuralgia (37), trigeminal neuralgia (38), and central NeuP (39). The analgesic effect is achieved by muscle paralysis, reduction of spasms, improvement of blood flow, and release of nerve fibers from compression caused by muscle contraction. Clinical studies conducted on a smaller number of patients showed very positive results, but it is necessary to further investigate the effectiveness of BoNT-A in the treatment of peripheral and central NeuP in a larger sample of patients.

Opioid analgesics in the treatment of neuropathic pain

Opioid analgesics, including drugs such as tramadol, oxycodone, and morphine, are a key therapeutic option in the treatment of cancer pain, and they are also used in the treatment of persistent chronic non-cancer pain of moderate to severe intensity. In clinical

practice, opioids are classified into weak (tramadol, codeine, dihydrocodeine) and strong (morphine, oxycodone, fentanyl, pethidine) analgesics, and the choice of drug depends on the degree of pain and the patient's response to therapy. Tramadol is a synthetic analgesic that acts as a weak agonist at mu (μ), kappa (κ), and delta (δ) opioid receptors. As a second-line analgesic, tramadol is useful in the treatment of acute and chronic pain conditions, and due to its dual mechanism of action, it stands out as the analgesic of choice in the treatment of pain with a neuropathic component (40). The recommended starting dose is 50-100 mg twice a day, and the dose is gradually increased to a maximum of 400 mg per day. Oxycodone is a strong analgesic, about twice as strong as morphine, and is used to treat moderate to severe pain. Oxycodone can be administered orally (often in combination with paracetamol), rectally, parenterally, and epidurally. The initial dose is 5-10 mg twice a day, and the drug is gradually titrated according to the patient's needs. Oxycodone is particularly useful in elderly patients, as it shows better tolerability and fewer side effects compared to morphine (41). Morphine is an opioid that represents the "gold standard" in pain therapy with an intensity greater than 6 on the numerical scale. It can be administered orally, rectally, subcutaneously, transdermally, intramuscularly, intravenously, epidurally, and intrathecally. The initial dose for oral administration is 10-30 mg twice daily, especially in elderly patients, and the dose is later titrated according to tolerability (42). Morphine is extremely effective in controlling pain but requires careful titration due to potential side effects.

Cannabinoids

Cannabinoids are used as an adjunct in a multicomponent pharmacotherapeutic concept in carefully selected patients with resistant pain (43). Cannabinoids are particularly useful in managing painful spasticity in multiple sclerosis, cachexia in HIV, and potential applications in the therapy of Parkinson's disease, Alzheimer's disease, cerebral ischemia, and other inflammatory diseases (44). However, the lack of randomized studies limits their widespread application.

Non-pharmacological treatment of neuropathic pain

Non-pharmacological treatment of NeuP is an important part of the overall therapeutic approach, which often serves as a complement to pharmacological treatments. Different methods of physical therapy are used in daily clinical practice, such as transcutaneous electrical nerve stimulation (TENS), electromagnetic therapy, low-intensity laser, massage, and kinesitherapy. These methods help reduce pain and improve patients' functionality. TENS is one of the most commonly used techniques, although clinical evidence for its effectiveness varies, it is often used due to the relatively low risk of side effects (45). Electromagnetic therapy and low-intensity lasers have the potential to improve circulation and reduce pain, but their use requires additional research to confirm long-term effectiveness. Physiotherapy, which includes specific exercises to improve muscle strength and flexibility, is also used to relieve symptoms of NeuP, especially when pain is associated with limited mobility. Psychological approaches, such as cognitive and behavioral therapy, are integrated into treatment plans because of their effectiveness in managing chronic pain. These methods help patients better understand and manage their pain, reducing emotional distress and improving quality of life (46). Although non-pharmacological treatment is often complementary to pharmacological interventions, it plays an important role in a holistic approach to NeuP therapy (47). All these methods should be adapted to the individual needs of patients, taking into account their specific symptoms, comorbidities, and preferences.

CONCLUSION

Neuropathic pain represents a serious therapeutic challenge, due to its complex pathophysiology and often refractory nature. Modern NeuP treatment combines pharmacological and non-pharmacological methods, with antidepressants, anticonvulsants, and opioids being key in pain control, while topical treatments and physiotherapy help to improve patients' functionality. Although pharmacological therapy is the mainstay, non-pharmacological techniques, including psychological approaches such as cognitive and behavioral therapy, play an important role in a comprehensive treatment approach. Educating patients and healthcare professionals about the nature of NeuP and available therapeutic options can significantly contribute to better control of this complex condition.

Abbreviation

IASP - International Association for the Study of Pain

NeuP - Neuropathic pain

VAS - Visual analog scale

NS - Numerical scale

VS - Verbal scale

DN4 - Douleur Neuropathique 4 Questions

S-LANSS - Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs

EMNG - Electromyoneurography

QST - Quantitative sensory testing
LEP - Laser-evoked potentials
CSF - Cerebrospinal fluid analysis
TCAs - Tricyclic antidepressants
HIV - Human Immunodeficiency Virus
TRPV1 - Transient receptor potentialreceptors
BoNT-A - Botulinum toxin
TENS - Transcutaneous electrical nerve stimulation

Author contribution:VM: Conceptualisation, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review and editing; RS: Conceptualisation, Validation, Writing - review and editing; VM: Conceptualisation, Investigation, Writing - review and editing.

Conflict of Interest: The authors declare no conflicts of interest related to this article.

NOTE: Artificial intelligence was not used as a tool in this study.

Funding: No.

Sažetak

NEUROPATSKI BOL: IZAZOVI I REŠENJA U KLINIČKOJ PRAKSI

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Neuropatski bol nastaje zbog abnormalne obrade signala u perifernom i centralnom nervnom sistemu. Karakteriše ga prisustvo bola bez spoljašnjeg nadražaja ili dugo nakon što je povreda prošla. Obično je hroničan, a pacijenti ga opisuju kao žarenje, peckanje, probadanje ili mravinjanje. Uzroci uključuju dijabetes, herpes zoster, hirurške intervencije, šlog, multiplu sklerozu, tumore i povrede. Uprkos značajnom napretku u istraživanju neuropatskog bola tokom poslednjih godina, terapijske mogućnosti ostaju ograničene i često nedovoljno efikasne. Simptomatska terapija neuropatskog bola se bazira na primeni lekova iz četiri osnovne grupe, a to su antidepresivi, antikonvulzivi, lokalni analgetici i opioidi. Pored farmakoloških metoda, u lečenju neuropatskog bola primenjuju se i nefarmakološke intervencije. Kombinacija ovih metoda sa farmakološkom terapijom često daje najbolje rezultate.

Ključne reči: Neuropatski bol, klinička slika, dijagnoza, terapija.

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***How to cite this article**:* **Mitrović V** Stolić R, Mitrović V. Neuropathic pain: chalanges and solutions in clinica practice. Sanamed. 2025; 20(1): 81-88. doi: 10.5937/sanamed0-56299.